c.) Remarks

As of this response, claims 1-20 remain pending. Independent claims 1, 5, 9, and 17 are amended herein. The following is a summary of the interview of May 16, 2006 between the applicants and the examiner.

Interview Summary

The applicants would like to thank the examiner for granting the interview of May 16, 2006. The interview participants were Examiner Henley and Gino Catena, attorney for applicants. In that interview, the applicants proposed an amendment to address the outstanding rejection under § 103(a) discussed below. The applicants proposed amending the independent claims to change the upper limit of the value of x from "less than 4.0" to "less than or equal to 3.95." The applicants discussed the significance of this change in light of the outstanding rejection, particularly in light of the teachings of Walsdorf `200. The details of the arguments made are provided below. The examiner was receptive to the arguments provided, but requested some independent, objective evidence to support the arguments offered by the applicants. The applicants provide such evidence herein in their detailed response.

Outstanding Rejections

The Examiner has entered or maintained the following objections/rejections:

1. Claims 1-20 are rejected under 35 USC § 103(a) as being unpatentable over U.S. Patent 5,432,200 to Walsdorf et al (hereinafter "Walsdorf `200") in view of Remington's Pharmaceutical Sciences (hereinafter "Remington").

Applicants address the rejection below.

1. Rejection of Claims 1-20 under 35 USC § 103(a) over Walsdorf `200 in view of Remington

The examiner has rejected claims 1-20 are rejected under 35 USC § 103(a) as being unpatentable over Walsdorf `200 in view of Remington. The examiner asserts that Walsdorf `200 teaches a salt of potassium, magnesium, and citrate having a potassium:magnesium:citrate ratio of "about" 4:1:2. The examiner asserts that the difference between the claimed subject matter and the disclosure of Walsdorf `200 is that Walsdorf `200 fails to teach the specific stoichiometric ratios of potassium, magnesium, and citrate of claims 1, 5, 9, and 17. Also, the examiner notes that the particular water content present in the hydrated mixture, as well as the physical constants of the prepared salt are not disclosed in Walsdorf `200 and that Walsdorf `200 fails to highlight spray drying as the process used to dry their composition. However, the examiner asserts that the subject matter sought to be patented would have been obvious to one of ordinary skill in the art at the time the invention was made because Walsdorf `200 teaches that the salt may have a potassium:magnesium:citrate ration of "about" 4:1:2. The examiner asserts that in the absence of evidence to the contrary, nothing unexpected is seen in varying the ratios of components in a manner specifically suggested by the reference. Pursuant to the interview between the examiner and applicants, the applicants amend claims 1, 5, 9, and 17.

The amendments to claims 1, 5, 9, and 17 change the upper limit of the value of x from "less than 4.0" to "less than or equal to 3.95." As amended, the independent claims are directed to a composition of potassium magnesium citrate having the general formula $K_xMg_y(C_6H_5O_7)_z$, wherein z is 2, and x is greater than or equal to 3.7 and less than or equal to 3.95 and y is greater than or equal to 1.0 and less than 1.15. The applicants believe that this amendment obviates any problems associated with Walsdorf `200. Although Walsdorf `200 refers to a potassium

magnesium citrate composition having a respective ratio of "about" 4:1:2 (Walsdorf '200 at col. 3, lns. 40-43), applicants note that in the context of the entire Walsdorf '200 disclosure, the "about" language of Walsdorf '200 is reasonably read by one or ordinary skill in the art to account for impurities. At col. 1, lns. 4-6, Walsdorf '200 recites:

> A new compound, a dual mineral salt, has now been synthesized by reacting stoichiometric quantities of citric acid, a magnesium compound and a potassium compound, preferably as follows... (emphasis added).

This teaching demonstrates that Walsdorf '200 is targeting the stoichiometric salt, in which the ratio is 4:1:2. This is further supported by the fact that nowhere in the Walsdorf '200 disclosure does Walsdorf '200 teach the use of less than the stoichiometric amount of potassium. Additionally, applicants note that the portion of the specification relied upon by the examiner is referring to the reaction mixture and not the final salt:

> The citric acid is mixed with water with uninterrupted agitation, and the magnesium compound and potassium compound are thereafter sequentially mixed with the citric acid to produce a dense, hydrated mixture. This dense hydrated mixture may be characterized as being a thick "slush" comprising potassium ions, magnesium ions and citrate ions in a proportion of about 4:1:2.

Walsdorf '200 at col. 3, lns. 35-43.

Additionally, Walsdorf '200 provides no data on the behavior of the compositions as the stoichiometry is varied. This is understandable because Walsdorf '200 is really only interested in the exact or near-exact stoichiometric compound. The only reasonable conclusion of one of ordinary skill in the art is that Walsdorf '200 uses the "about" language to account for impurities in the starting materials which could result is ratios slightly deviating from 4:1:2. Notably, where Walsdorf '200 uses the "about" language, it does so in the context of a hydrated mixture, which it further characterizes as a "thick slush."

In contrast, the present invention is directed to a composition having a specific stoichiometry distinct from the stoichiometric molar composition of 4:1:2. The instant specification provides analytical data demonstrating the effects of modifying the K:Mg stoichiometry and makes clear that it is directed to the distinct composition having a K:Mg ratio of less than 4.0 and preferably less than 3.95. As discussed in the interview with the examiner, FIG. 11 of the instant specification shows the difference between the claimed composition and the composition of the prior art (Walsdorf `200). With the current amendments, the claimed compound is a distinct compound at a K:Mg ratio less than or equal to 3.95. A phase transition occurs at this value (and continues at higher values) which is the prior art composition and includes the stoichiomtrically exact potassium magnesium citrate.

While the applicants believe the teachings of the instant specification are novel and nonobvious over that of Walsdorf `200, in light of the recitation in Walsdorf `200 of a ratio of "about 4:1:2", applicants believe that it is appropriate to amend the upper range of the K:Mg ratio from "less than 4.0" to "less than or equal to 3.95." While applicants believe that one of ordinary skill in the art would read the recitation of Walsdorf `200 to account for only impurities, the original claim limitation range may read on an impure pharmaceutical composition of potassium magnesium citrate. Amending the upper limit to 3.95 requires a greater than 1% deviation from the stoichiometric salt. One of ordinary skill in the art would not expect a greater variability in purity for an active pharmaceutical ingredient. As evidence in support of this assertion, applicants provide copies of monographs of various potassium salts from the electronic edition of the 29th edition of the United States Pharmacopeia (USP 29/NF24). Monographs for potassium citrate, potassium chloride, potassium carbonate, potassium bicarbonate potassium acetate are provided. Applicants could not find a monograph for potassium magnesium citrate

and do not believe that such a monograph exists. What is noteworthy about each of these monographs is that they require a lower purity limit of no less than 99.0%. The monograph for potassium citrate is particularly instructive as it is the closest compound to potassium magnesium citrate. A lower purity limit of 99.0% is given for potassium citrate. Accordingly, one of ordinary skill in the art would not expect a purity of a pharmaceutical potassium salt to have more than 1.0 % of impurities.

Because Walsdorf `200 does not teach or suggest a potassium magnesium citrate composition differing significantly from the stoichiometrically exact 4:1:2 ratio of K:Mg:Citrate, it is only reasonable to conclude that that "about" language used by Walsdorf `200 is concerned with impurities only. Because both Walsdorf `200 and the instant invention are concerned with pharmaceutical potassium magnesium citrate, it is also reasonable that any deviations due to impurities would be small. Accordingly, applicants assert that the amendments made herein to the pending independent claims sufficiently distinguish the claimed composition over that of Walsdorf `200. Figure 11 of the instant specification, clearly shows a phase transition at K:Mg ratios beginning no lower than 3.95, indicative of distinct compositions on either side of the transition. Applicants believe that the lower ratio composition is novel and nonobvious over the teachings of Walsdorf `200, notwithstanding the Walsdorf `200 recitation of "about 4:1:2."

In light of the amendments and arguments provided herein and in light of the interview between applicants and the examiner of May 16, 2006, applicants believe that the claims are now in condition for allowance. Accordingly, applicants respectfully request that the examiner withdraw the outstanding rejection.

d.) Conclusions

In light of the arguments and amendments made herein, Applicants respectfully assert that the pending claims are in condition for allowance. Because the Examiner's rejections have been addressed, Applicants respectfully request withdrawal of the outstanding rejections. Accordingly, Applicants earnestly request allowance of the pending claims. This is intended to be a complete response. If any issues remain outstanding, please contact the undersigned for resolution of the same.

Applicants believe that no fees are due or associated with the filing of this document. However, if Applicants are in error, the Commissioner is hereby authorized to draw any additional fees associated with this filing from Deposit Account No. 06-2375, under Order No. P02655US0/10209733 from which the undersigned is authorized to draw.

Respectfully submitted,

Date: May 19, 2006

By: Gino Catena

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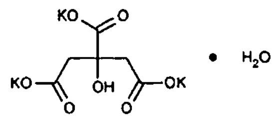
Enclosure: 6 pages – Title: Potassium Citrate



Potassium Citrate

$C_6H_5K_3O_7 \cdot H_2O$ 324.41
1,2,3-Propanetricarboxylic acid, 2-hydroxy-, tripotassium salt, monohydrate.
Tripotassium citrate monohydrate [*6100-05-6*].
Anhydrous 306.40 [*866-84-2*].

» Potassium Citrate contains not less than 99.0 percent and not more than 100.5 percent of $C_6H_5K_3O_7$, calculated on the dried basis.

Packaging and storage— Preserve in tight containers.

Identification— A solution (1 in 10) responds to the tests for *Potassium* ⟨191⟩ and for *Citrate* ⟨191⟩.

Alkalinity— A solution of 1.0 g in 20 mL of water is alkaline to litmus, but after the addition of 0.20 mL of 0.10 N sulfuric acid, no pink color is produced by the addition of 1 drop of phenolphthalein TS.

Loss on drying ⟨731⟩ — Dry it at 180° for 4 hours: it loses between 3.0% and 6.0% of its weight.

Tartrate— To a solution of 1 g in 1.5 mL of water in a test tube add 1 mL of 6 N acetic acid, and scratch the walls of the test tube with a glass rod: no crystalline precipitate is formed.

Heavy metals, *Method I* ⟨231⟩— Dissolve 2 g in 25 mL of water, and proceed as directed for *Test Preparation*, except to use glacial acetic acid to adjust the pH: the limit is 0.001%.

Organic volatile impurities, *Method I* ⟨467⟩: meets the requirements.

Assay— Dissolve about 200 mg of Potassium Citrate, accurately weighed, in 25 mL of glacial acetic acid. Add 2 drops of crystal violet TS, and titrate with 0.1 N perchloric acid VS to a green endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 10.21 mg of $C_6H_5K_3O_7$.

Auxiliary Information—

Staff Liaison : Lawrence Evans, Ph.D., Senior Scientific Associate

Expert Committee : (DSN) Dietary Supplements: Non-Botanicals
Phone Number : 1-301-816-8389

Potassium Chloride

KCl 74.55

Potassium chloride.

Potassium chloride [*7447-40-7*].

» Potassium Chloride contains not less than 99.0 percent and not more than 100.5 percent of KCl, calculated on the dried basis.

Packaging and storage— Preserve in well-closed containers.

Labeling— Where Potassium Chloride is intended for use in hemodialysis, it is so labeled.

Identification— A solution (1 in 20) responds to the tests for *Potassium* □⟨ 191□⟩ and for *Chloride* □⟨ 191□⟩.

Acidity or alkalinity— To a solution of 5.0 g in 50 mL of carbon dioxide –free water add 3 drops of phenolphthalein TS: no pink color is produced. Then add 0.30 mL of 0.020 N sodium hydroxide: a pink color is produced.

Loss on drying □⟨ 731□⟩ — Dry it at 105° for 2 hours: it loses not more than 1.0% of its weight.

Iodide or bromide— Dissolve 2 g in 6 mL of water, add 1 mL of chloroform, and then add, dropwise, with constant agitation, 5 mL of a mixture of equal parts of chlorine TS and water: the chloroform is free from even a transient violet or a permanent orange color.

Aluminum □⟨ 206□⟩ (where it is labeled as intended for use in hemodialysis) — Proceed as directed using 2.0 g of Potassium Chloride to prepare the *Test Preparation:* the limit is 1 µg per g.

Calcium and magnesium— To 20 mL of a solution (1 in 100) add 2 mL each of 6 N ammonium hydroxide, ammonium oxalate TS, and dibasic sodium phosphate TS: no turbidity is produced within 5 minutes.

Sodium— A solution (1 in 20), tested on a platinum wire, does not impart a pronounced yellow color to a nonluminous flame.

Heavy metals □⟨ 231□⟩ — Dissolve 2.0 g in 25 mL of water: the limit is 0.001%.

Organic volatile impurities, *Method I* □⟨ 467□⟩ : meets the requirements.

Assay— Dissolve about 200 mg of Potassium Chloride, accurately weighed, in 10 mL of water. Add 10 mL of glacial acetic acid, 75 mL of methanol, and 3 drops of eosin Y TS. Titrate, with shaking, with 0.1 N silver nitrate VS to a pink endpoint. Each mL of 0.1 N silver nitrate is equivalent to 7.455 mg of KCl.

Auxiliary Information—

Staff Liaison : Karen A Russo, Ph.D., Scientist

Expert Committee : (PA1) Pharmaceutical Analysis 1

Phone Number : 1-301-816-8379

Potassium Carbonate

K_2CO_3 (anhydrous) 138.21

Carbonic acid, dipotassium salt.

Dipotassium carbonate [*584-08-7*].
Sesquihydrate 165.23

» Potassium Carbonate contains not less than 99.5 percent and not more than 100.5 percent of K_2CO_3, calculated on the dried basis.

Packaging and storage— Preserve in well-closed containers.

Identification— It responds to the tests for *Potassium* □⟨ 191□⟩ and for *Carbonate* □⟨ 191□⟩.

Loss on drying □⟨ 731□⟩ — Dry it at 180° for 4 hours: it loses not more than 0.5% of its weight.

Insoluble substances— Dissolve 1 g in 20 mL of water: the solution is complete, clear, and colorless.

Heavy metals □⟨ 231□⟩ — Dissolve 4.0 g in 10 mL of water, add 15 mL of 3 N hydrochloric acid, and heat to boiling. Add 1 drop of phenolphthalein TS, and neutralize with 1 N sodium hydroxide until the solution is faintly pink in color. Cool, and dilute with water to 25 mL: the limit is 0.0005%.

Organic volatile impurities, *Method I* □⟨ 467□⟩ : meets the requirements.

Assay— Transfer the dried potassium carbonate obtained in the test for *Loss on drying* to a flask with the aid of 150 mL of water, add 4 drops of methyl orange TS, and titrate with 1 N hydrochloric acid VS. Each mL of 1 N hydrochloric acid is equivalent to 69.11 mg of K_2CO_3.
Auxiliary Information—
Staff Liaison : Andrzej Wilk, Ph.D., Senior Scientific Associate

Expert Committee : (PA5) Pharmaceutical Analysis 5

Phone Number : 1-301-816-8305

Potassium Bicarbonate

$KHCO_3$ 100.12

Carbonic acid, monopotassium salt.

Monopotassium carbonate   *[298-14-6]*.

» Potassium Bicarbonate contains not less than 99.5 percent and not more than 101.5 percent of $KHCO_3$, calculated on the dried basis.

Packaging and storage— Preserve in well-closed containers.

Identification— A solution (1 in 10) responds to the tests for *Potassium* ⟨191⟩ and for *Bicarbonate* ⟨191⟩.

Loss on drying ⟨731⟩ — Dry it over silica gel for 4 hours: it loses not more than 0.3% of its weight.

Normal carbonate— Grind 3.0 g of Potassium Bicarbonate with 25 mL of alcohol and 5 mL of water in a porcelain mortar. Add 3 drops of phenolphthalein TS, and titrate slowly with barium chloride solution, prepared by dissolving 12.216 g of barium chloride in 300 mL of water and diluting with alcohol to obtain 1000 mL of solution, until the suspension becomes colorless. Continue the grinding for 2 minutes, and if the color turns pink, continue the titration with the barium chloride solution to a colorless end-point. Repeat the grinding for 2 minutes and the addition of the barium chloride solution, if necessary, until the suspension is colorless after 2 minutes of grinding. Each mL of the barium chloride solution is equivalent to 6.911 mg of K_2CO_3: not more than 2.5% is found.

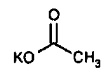
Heavy metals, *Method I* ⟨231⟩**—** To 2 g add 5 mL of water and 8 mL of 3 N hydrochloric acid, heat to boiling, and maintain that temperature for 1 minute. Add 1 drop of phenolphthalein TS and sufficient 6 N ammonium hydroxide, dropwise, to give the solution a faint pink color. Cool, add 2 mL of 1 N acetic acid, and then dilute with water to 25 mL: the limit is 0.001%.

Organic volatile impurities, *Method IV* ⟨467⟩ : meets the requirements.

Assay— Dissolve about 4 g of Potassium Bicarbonate, accurately weighed, in 100 mL of water, add methyl red TS, and titrate with 1 N hydrochloric acid VS. Add the acid slowly, with constant stirring, until the solution becomes faintly pink. Heat the solution to boiling, cool, and continue the titration until the pink color no longer fades after boiling. Each mL of 1 N hydrochloric acid is equivalent to 100.1 mg of $KHCO_3$.

Auxiliary Information—

Staff Liaison : Karen A Russo, Ph.D., Scientist
Expert Committee : (PA1) Pharmaceutical Analysis 1
Phone Number : 1-301-816-8379



Potassium Acetate

$C_2H_3KO_2$ 98.14
Acetic acid, potassium salt.
Potassium acetate [*127-08-2*].

» Potassium Acetate contains not less than 99.0 percent and not more than 100.5 percent of $C_2H_3KO_2$, calculated on the dried basis.

Packaging and storage— Preserve in tight containers.

Identification— A solution (1 in 10) responds to the tests for *Potassium* ⟨191⟩ and for *Acetate* ⟨191⟩.

pH ⟨791⟩: between 7.5 and 8.5, in a solution (1 in 20).

Loss on drying ⟨731⟩ — Dry it at 150° for 2 hours: it loses not more than 1.0% of its weight.

Heavy metals, *Method I* ⟨231⟩— Prepare the *Test Preparation* as follows. Dissolve 1 g in 10 mL of water, add 3.0 mL of glacial acetic acid, dilute with water to 25 mL, and adjust with glacial acetic acid to a pH between 3.8 and 4.0, measured with a pH meter. Prepare the *Monitor Preparation* as directed for *Test Preparation*, 2.0 mL of *Standard Lead Solution* being added: the limit is 0.002%.

Change to read:
Limit of sodium—
Potassium chloride solution— Dissolve 100 g of potassium chloride in water to make 1000 mL.
Standard solutions— Transfer 127.1 mg of sodium chloride, previously dried at 105° for 2 hours and accurately weighed, to a 500-mL volumetric flask, add water to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 2.0, 5.0, and 10.0 mL of this solution to separate 100-mL volumetric flasks, add 10.0 mL of *Potassium chloride solution* to each flask, dilute with water to volume, and mix. These *Standard solutions* contain 0.2, 0.5, and 1.0 µg of sodium per mL, respectively. [NOTE — Concentrations of sodium in the *Standard solutions* may be modified to fit the linear or working range of the atomic absorption spectrophotometer.]
Test solution— Transfer about •0.2•1S (*USP26*) g of Potassium Acetate, accurately weighed, to a 100-mL volumetric flask containing about 50 mL of water, and swirl to dissolve. Add 10.0 mL of *Potassium chloride solution*, dilute with water to volume, and mix. [NOTE — The concentration of Potassium Acetate in the *Test solution* may be modified by using a different quantity or by further dilution to bring the absorption response within the range of responses obtained from the *Standard solutions*.]
Blank solution— Transfer 10.0 mL of *Potassium chloride solution* to a 100-mL volumetric flask, dilute with water to volume, and mix.
Procedure— Concomitantly determine the absorbances of the *Standard solutions* and the *Test solution* at the sodium emission line of 589 nm, with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a sodium hollow-cathode lamp and an oxidizing air-acetylene flame, using the *Blank solution* to zero the instrument. Plot the absorbances of the *Standard solutions* versus concentration, in µg per mL, of sodium, and draw the straight line best fitting the plotted points. From the graph so obtained, determine the concentration *C*, in µg per mL, of sodium in the *Test solution*. Calculate the percentage of sodium in the portion of Potassium Acetate taken by the formula:

$$CD / 10{,}000W,$$

in which *W* is the quantity, in g, of Potassium Acetate taken to prepare the *Test solution;* and *D* is the extent of dilution of the *Test solution:* not more than 0.03% of sodium is found.

Assay— Dissolve about 200 mg of Potassium Acetate, previously dried and accurately weighed, in 25 mL of glacial acetic acid, add 2 drops of crystal violet TS, and titrate with 0.1 N perchloric acid VS to a

green endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 9.814 mg of $C_2H_3KO_2$.

Auxiliary Information—

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Expert Committee : (PA6) Pharmaceutical Analysis 6
Phone Number : 1-301-816-8389